EMERGING INTERNATIONAL CONTAMINANT ISSUES:

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Development of Codex Alimentarius standards to address the issues.

The Codex Alimentarius Commission (CAC) is a longstanding international food standards organization whose aim is to develop consensus standards to protect consumer health and ensure fair trade practices. In 1994, the World Trade Organization (WTO) was established, which lays out a broad framework for international trade policies. The WTO established the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), specifically recognizing CAC as the body responsible for developing international food safety standards. The SPS Agreement essentially presumes that Codex Alimentarius standards provide a sufficient level of protection. SPS measures must be based on scientific principles and on risk assessment. Further, the WTO agreements recognize that each country may determine the appropriate level of public health protection for its own population.

The CAC responded very quickly to the 1994 WTO agreements with a statement on the role of science, averring that standards must be based on sound scientific principles, and where appropriate, that other legitimate factors relevant to health protection of consumers and promotion of fair trade practices should be considered. The CAC also adopted a statement of principles on the role of food safety risk assessment based on a series of expert consultations that laid the framework for risk analysis. The CAC defines risk analysis as the triumvirate of risk assessment, management and communication. The CAC also recommended that all Codex committees should continue to develop and apply risk analysis principles and methodologies appropriate to their specific mandates.

In this article, we will focus on the emerging international food contaminant issues and the development of CAC standards to address those issues.

RISK ASSESSMENT OF CONTAMINANTS

The main purpose of the Codex Committee on Food Additives and Contaminants (CCFAC) is to establish standards, maximum levels allowed for contaminants and food additive levels, as well as other standards and codes of practice. The group also sets priorities for evaluation by the Joint Expert Committee on Food Additives (JECFA), the scientific advisory committee to CCFAC, for toxicological evaluations. JECFA prepares contaminant and additive toxicological monographs and is the body responsible for conducting risk assessments and setting food additive composition specifications. Presently, the CCFAC is laying the foundation for the respective roles of CCFAC and JECFA and how they interact. Essentially, CCFAC is responsible for setting risk assessment policy and managing risk, while JECFA performs the actual risk assessments.

CCFAC has adopted a general standard for contaminants, including the preamble adopted in 1995, which contains definitions, principles, criteria for toxicological, analytical and intake data, fair trade, risk assessment, risk management and procedures. The annexes to the general standard elaborate on some of the preamble issues, such as the criteria for establishing maximum levels (MLs) and procedures for risk management decisions. This basically provides for a sound scientific basis when considering risk assessment and fair trade practices that will be used by the committee in performing its risk management work.

In a paper on methodology and principles for exposure assessment of contaminants, which has been before the committee in various forms since 1996, the United Kingdom presented a procedure for deriving MLs. This paper went beyond the exposure assessment objective to describing a procedure for setting MLs. This past year, the procedure was tested on setting MLs for lead, using adults as the end point. Of course, children, not adults, are really the end point for lead. Further, lead is a difficult risk assessment problem and is not a good candidate for testing these procedures. We see the utility of such a process as primarily a "screening tool." If one can figure out what MLs are feasible internationally and, based on a simple safety assessment approach, the contaminant safe exposure levels are within these levels, then one could basically establish those MLs and be done. However, if a complicated situation arises, the scientific advising body, JECFA, will be asked to do a risk assessment and advise the CCFAC to inform its risk management decisions. There was a great deal of concern in the committee that this document was too complicated, that it should be simplified, and thus, they're back to redrafting it, particularly looking at the intent and objectives. It is intended as an annex to the general standard. There are probably going to be some procedures for allocating MLs in this document.

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Ochratoxin A	U.S.
Cadmium	Japan, U.S.
Dioxins and Dioxin-like PCBs	CCFAC
Fumonisins	U.S., IPCS
Chloropropanols	U.S.
Ethyl Carbamate	CCFAC
Glycyrrhizic Acid	Denmark
Nitrate	The Netherlands
Phenylhydrazines (including Agaritine)	Denmark
Polycyclic Aromatic Hydrocarbons	Denmark, Canada, The Netherlands
Tin (acute reference dose)	CCFAC
Trichothecenes (including T2 and DON)	The Netherlands, China

Table 1. 1999 contaminant and naturally occurring toxin priority list for JECFA evaluation.

Therefore, it is going to be an important piece for laying the foundation for how CCFAC develops standards.

What are the U.S. themes in dealing with CCFAC contaminant issues? First, the standard-setting work has to be based on science and risk assessment. Second, prevention is the best public health control, and therefore we strongly support codes of practice that aim to prevent or minimize contamination. Third, the U.S. generally agrees that no international standard is really needed for a contaminant, unless there is international trade problem. Of course, even without a national standard, we can always address a public health problem in the U.S. at any time using a case-by-case approach under the Federal Food, Drug and Cosmetic Act mandates. Fourth, MLs can be based on a negligible-risk safety assessment approach, where feasible. In most cases, in contrast to food additives, when contaminants become an issue, their exposure is generally too high to be feasible for countries to meet safety assessment derived levels. At this point, a risk assessment is needed. One must consider the risk without intervention, the risk reduction and the feasibility for each risk management option and work from there to determine the best approach to reduce the risk from the contaminant. As far as how we consider feasibility in the U.S., we presume that the production is under Good Agriculture Practices (GAPs) and Good Manufacturing Practices (GMPs) before allowance is made for feasibility. Another major issue that colors the kind of data used in developing these maximum levels is that the contaminant data need to be quality data derived under good agriculture and manufacturing conditions.

As mentioned, CCFAC establishes priority lists for JECFA food contaminant risk evaluation (Table 1). This list provides a snapshot of the things to come. The highest four priority contaminants are ochratoxin A, cadmium, dioxin and fumonisins. Fumonisins are mycotoxins that will be drawing serious attention internationally in the near future and are scheduled for a JECFA risk assessment in February 2000. On the list are chemicals such as ethyl carbamate, on which the U.S. is currently doing a bioassay. It's likely to become a significant subject both in the U.S. and for the CCFAC once the study is completed. Also, trichothecenes, such as deoxynivalenol (DON), which can adversely affect wheat and barley, are another emerging area of interest. DON, T-2 and HT-2 toxins are scheduled for JECFA review in February 2000.

Priority Contaminants

The following contaminants are currently under review by CCFAC.

Ochratoxin A. This mycotoxin is generally found in cereals, mainly wheat and barley. Ochratoxin A is also found in coffee, wine, pork and grapes. One of the problems in establishing MLs for ochratoxins is that there is very little international data outside of Europe. In order to establish a realistic international level, we need to gather data from a much wider geographical area over several years, especially since mycotoxin levels vary substantially from year to year. CCFAC has agreed that a code of practice should be developed and this is now underway.

In addition, there is genuine disagreement about the carcinogenic potential of ochratoxin exposure to humans. While ochratoxin A is reported to produce hepatic and renal tumorrs in some animal bioassays, the mechanism by which this may occur is unknown. For example, ochratoxin does produce pronounced renal toxicity and it is quite plausible that any carcinogenic event occurs as a secondary response to renal toxicity, and not because ochratoxin has inherent genotoxic activity. The relevant public health end point, whether it is carcinogenesis or any other toxic effect, is very much dependent on the frequency and level of plausible human exposures. If exposures are intermittent and high, then an effect on renal function may be the most relevant end point; whereas, if exposures are constant, long-term and at a low level, then a chronic effect like carcinogenesis will need to be considered. This issue is absolutely critical in ultimately determining the reasonable level of human exposure. In its last deliberation, JECFA selected renal toxicity as the critical effect and used it as the basis for deriving a tolerable level of exposure. In subsequent deliberations, JECFA will have to address the carcinogenic potential of ochratoxin A exposure, much like it did with aflatoxin.

CCFAC also adopted a draft ML at Step 3 of 5 ppb for ochratoxin A. It is not clear why this level is more appropriate than others, for example, 2 ppb, 10 ppb or 20 ppb. Therefore, it is important for JECFA to address the risk assessment, because a level of 5 ppb may cause major disruptions in international trade and we need to understand what the public health benefits are compared to the feasibility of attaining these various levels. Ochratoxin A is scheduled for JECFA evaluation in February 2000.

Zearalenone. This mycotoxin is a fairly recent addition to the committee's list of contaminant considerations and is found on corn and wheat. JECFA performed a zearalenone safety assessment this year and established a provisional tolerable daily intake (PTDI) of 0.5 mg/kg per day, which is much higher than the Canadian and Nordic level of 0.1 mg/kg. The Canadian and Scandinavian intakes are predicted to be lower than those PTDIs. It is not clear whether JECFA will establish an ML for zearalenone. When

the U.S. looked at the incidence of this contaminant in 1985 and 1989, the incidence rate was approximately 20% with mean levels around 20 ppb. There are eight countries that have levels set ranging from 30 ppb up to 1 ppm. The lower levels could present a trade problem.

Patulin. This is a mycotoxin that shows up in apple juice if damaged or rotten apples are used in its manufacture. The key here is that patulin is controllable by culling bad fruit. Two years ago, the U.S. presented a rationale to CCFAC that a 50 ppb ML would meet JECFA's provisional tolerable daily intake (0.43 µg/kg/day). JECFA's level was based on a chronic study using a 100-fold safety factor to establish negligible risk. The exposure assessment demonstrated that it would be protective of public health, even considering high-consuming children (given that consumption of over 400 mL a day meets roughly a 100-fold safety factor).

The U.S. advocated accelerating the process to Step 8. We believe that this is a rare case in which an international level can easily be set for a contaminant since it is feasible to control levels by simply culling out bad fruit. The U.S. also considered this an opportunity to put a standard in place to solve the problem indicated by our data that a substantial amount of apple juice exceeding the 50 ppb level is shipped to the U.S. and offered to manufacturers. Some countries believe, however, that the level ought to be lower, specifically 25 ppb, citing mixed results on mutagenicity. These countries also remain concerned about children's exposure and further believe that 25 ppb is feasible. This issue was forwarded to the CAC and adopted at Step 5 in June 1999. In the meantime, FDA presented this to its Food Advisory Committee, which agreed that 50 ppb would be protective of public health. FDA is proceeding to issue a 50 ppb action level.

Lead. Moving out of the mycotoxin area, lead has been under discussion for a long time and draft MLs were adopted by CCFAC at Step 5 in 1997. The really interesting thing about developing these levels is that the exposure of adults was the reference point, never the exposure of children. The U.S. has continuously stressed that young children are the sensitive population; levels should not be adopted without considering relatively short-term exposures to infants, toddlers and small children. There is no known "no-effect" level for lead; the adverse cognitive effects are seen even at blood lead levels of less than 10 µg/dL. In 1999, there was a first attempt by CCFAC to address children's exposure. Further, this very complicated situation was again reviewed by JECFA and a quantitative risk assessment was completed in June 1999. JECFA retained its previous 25 mg/kg provisional tolerable weekly intake. However, JECFA did recognize that low blood levels could lead to adverse cognitive effects, but JECFA was not generally concerned based on the data they had received (primarily from developed countries) about the levels to which consumers were being exposed. At a March 1999 CCFAC meeting, some countries wanted to finalize the MLs at Step 8 *before* JECFA did its quantitative risk assessment in June 1999.

Table 2 provides a list of many of the proposed lead MLs. Some of the foods that are of particular concern to the U.S., specifically in light of children's exposures, are wheat, milk, fish and fruit juice. Based on data for commodities grown on uncontaminated crop land, the U.S. doesn't believe that wheat lead levels should be more than 0.1 ppm. Milk, although it presents detection difficulties, should not contain lead at levels higher than 5 ppb. There has been some interest in moving the level for fish higher than 0.2 ppm and, considering children's consumption of particular fish, such as tuna, perhaps some thought should be given to setting two levels for fish. There is still some pressure to move the 0.05 ppm ML for fruit juice back up to 0.1 ppm. Again the U.S. is concerned about increasing the juice levels because of the high level of consumption by children.

Fruit	0.1 ppm Numbers for Previous Year's Commodities	
Small Fruit and Berries	[0.3]	
Vegetables	0.1	
Brassica, Leafy Vegetables	0.3	(also mushrooms)
Cereal Products	0.2	(except bran)
Pulses, Legumes	0.2	
Meat and Fats	0.05	0.1 (98)
Milk and Infant Formula	0.02	
Fish	0.2	0.5 (98)
Fruit Juice	0.05	0.1 (98)

Table 2. Some proposed lead maximum levels at Step 6.

Tin. This metal is purposely used in unlacquered cans to prevent oxidative browning and to ensure can integrity for products such as peaches, pears, pineapple and tropical fruits. In certain cases, where temperatures are high enough, the product is held long enough and excessive nitrates are present, very high levels of tin can leach into the product. This can cause gastric irritation, and although this is not a severe hazard, it does cause some people to become sick. While tin is used in the U.S. as a food additive, it is viewed as a contaminant by CCFAC. As a contaminant, many countries consider that the draft MLs of 200 ppm for liquid canned foods and 250 ppm for solid canned foods are not the lowest levels achievable. If coated cans are used, much lower levels are achievable. So they really are not considering the technological need. CCFAC determined that JECFA needs to look at the acute toxicity to inform its risk management (scheduled for JECFA review in June 2000). It was also sent to the CAC for adoption at Step 5. The CAC adopted 200 ppm in liquid canned foods and 250 ppm in solid canned foods, but it is being held at that step until JECFA completes its evaluation.

Arsenic. Arsenic shows up in a variety of forms. Inorganic arsenic is the most toxic form. Most of the arsenic detected is found in seafood, where the organic, relatively nontoxic arsenobetaine form predominates. The National Academy of Sciences (NAS) recently recommended to the U.S. Environmental Protection Agency (EPA) that it reduce the maximum contaminant level (MCL) of arsenic in

Fruit	0.05 ppm	Numbers for Previous Year's Commodities
Vegetables (including potatoes)	0.05	(98 - 0.1)
Leafy Vegetables	0.2	
Wheat Grain and Rice	0.2	
Soybeans and Peanuts	0.2	
Meat (cattle, poultry, pig, sheep)	0.05	(98 - 0.1)
Meat (horse)	0.2	(98 - 0.5)
Liver (cattle, poultry, pig, sheep)	0.5	
Kidney (cattle, poultry, pig, sheep)	1.0	
Crustaceae	0.5	

Table 3. Proposed draft cadmium maximum levels at Step 3.

drinking water as soon as possible. The current MCL for drinking water, which is predominantly inorganic, is 50 ppb. The World Health Organization (WHO) has already established a 10 ppb level.

The CCFAC has agreed that arsenic levels in the typical diet do not present a public health concern, although we all will take a close look at the recent NAS report. The primary obstacle CCFAC faces in proceeding with establishing any kind of ML is that analytical methods aren't really available, and they're clearly not routine, for differentiating the species and determining the inorganic arsenic levels. As such, the CCFAC has put development of arsenic MLs on hold until some future date, though probably not too far down the road.

Cadmium. The key problem caused by cadmium in food is nephrotoxicity due to long-term accumulation in the kidneys. It is found in all foods at various levels. The draft MLs under consideration by CCFAC are shown in Table 3. The typical exposure is around 25 µg/day, although in the U.S. it is quite a bit lower (≤12 µg/day). High consumption of foods that contain relatively high cadmium levels can be a problem, because these extreme exposures are quite close to where deleterious effects actually occur. But in order to set levels, one really has to look at bioavailability. Because of other microelements like zinc in products such as spinach and oysters, cadmium bioavailability is very low and that has to be taken into consideration. There are studies underway on sunflower kernels and rice relating to cadmium bioavailability and its effects. Several years ago, the U.S. and Japan placed cadmium on the JECFA priority list for risk assessment. JECFA will evaluate cadmium in June 2000. In the meantime, like with ochratoxin A, CCFAC has decided to again adopt levels at Step 3. There was substantial disagreement on moving this forward without JECFA's input. Data on commodities grown on uncontaminated crop lands were presented to the drafters of the discussion paper by the U.S. But in spite of this data, several of the proposed levels were set too low, specifically 0.05 ppm for carrots and potatoes. If U.S. commodity data are representative of the food supply across the country, the data indicate that 18% of our carrots and 14% of our potatoes (grown in uncontaminated soils) contain cadmium at levels above the proposed ML adopted at Step 3. There is also much discussion about whether countries will be able to meet the meat level of 0.05 ppm.

Dioxins. Long considered one of the most problematic contaminants, dioxins are found in a wide variety of foods as the result of environmental contamination or from natural sources. The most recent highly publicized "dioxin" contamination episode in Belgium is alleged to be a criminal polychlorinated biphenyl (PCB) contamination of fat used in animal feeds that affected poultry, cows, pigs and their products. Dioxins are highly fat soluble, thus accumulating in fatty tissues in animals and fish. They are an extremely potent collection of related chlorinated dibenzo-dioxins and dibenzofurans and cause a spectrum of adverse effects in study animals, including cancer and endocrine effects.

There is a great deal of concern in the committee that it is premature to set MLs because some basic changes in how countries deal with emissions from smokestacks must first be made to reduce levels of dioxins in the environment. The other key problem is, of course, the lack of practical analytical methods. While an ion trap MS/MS method was recently developed at the FDA that reduces analytical time by two-thirds, there are still the problems posed by analysis at the 1 ppt level. This is neither routine nor easily achievable in international trade, making international MLs difficult to apply.

Presently, CCFAC is gathering information on dioxins, but we expect the European Union countries to push for international MLs. In May 1998, a European WHO group performed a safety assessment reevaluation, establishing a TDI range of 1-4 picogram toxic equivalents per kilogram using an uncertainty factor of 10. CCFAC has asked JECFA to give high priority to the evaluation, and we believe that a quantitative risk assessment is important to conduct at this point.

Conclusion

The U.S. is working very hard to ensure a scientific process and to ensure that risk assessment is brought to bear on establishing proper international standards for food contaminants. CCFAC foundation documents are crucial tools to ensure the use of science in the standard-setting process. Quality data is needed in order to set proper MLs. Further, the data must be derived from products that are manufactured under GAPs and GMPs. Clearly, the U.S. needs more data to support its work. The bottom line is to expect numerous international maximum levels for food contaminants to be set. Although the process may be slow, these standards are coming, they're with us, and people need to be engaged in this process from all countries and all industries, because it will be a fact of life.

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